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Genome-wide association meta-analysis identifies new endometriosis risk loci

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URLs.

A Catalog of Published Genome-Wide Association Studies, www.genome.gov/gwastudies;

Gene Expression Omnibus (GEO) database, <http://www.ncbi.nlm.nih.gov/gds/>;

GENe Expression VARIation (Genevar) database, <http://www.sanger.ac.uk/resources/software/genevar/>;

GWAMA, <http://www.well.ox.ac.uk/gwama/>;

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Abstract

We conducted a genome-wide association (GWA) meta-analysis of 4,604 endometriosis cases and 9,393 controls of Japanese¹ and European² ancestry. We show that rs12700667 on chromosome 7p15.2, previously found in Europeans, replicates in Japanese ($P = 3.6 \times 10^{-3}$), and confirm association of rs7521902 on 1p36.12 near *WNT4*. In addition, we establish association of rs13394619 in *GREB1* on 2p25.1 and identify a novel locus on 12q22 near *VEZT* (rs10859871). Excluding European cases with minimal or unknown severity, we identified additional novel loci on 2p14 (rs4141819), 6p22.3 (rs7739264) and 9p21.3 (rs1537377). All seven SNP effects were replicated in an independent cohort and produced $P < 5 \times 10^{-8}$ in a combined analysis. Finally, we found a significant overlap in polygenic risk for endometriosis between the European and Japanese GWA cohorts ($P = 8.8 \times 10^{-11}$), indicating that many weakly associated SNPs represent true endometriosis risk loci and risk prediction and future targeted disease therapy may be transferred across these populations.

Endometriosis (MIM131200) is a common gynecological disease associated with severe pelvic pain, affecting 6-10% of women in their reproductive years^{3,4} and 20-50% of women with infertility⁵. Endometriosis risk is influenced by genetic factors and has an estimated heritability of around 51%³.

Two large endometriosis GWA studies^{1,2} have reported genome-wide significant associations. The first, in a Japanese sample of 1,423 cases and 1,318 controls obtained from the BioBank Japan (BBJ), with 484 cases and 3,974 controls for replication, implicated a SNP (rs10965235) in the *CDKN2BAS* gene on chromosome 9p21.3 (overall odds ratio (OR) = 1.44, 95% CI 1.30–1.59; $P = 5.57 \times 10^{-12}$)¹. The second, by the International Endogene Consortium (IEC) in a sample of European ancestry from Australia (2,270 cases and 1,870 controls) and the UK (924 cases and 5,190 controls), with 2,392 cases and 2,271 controls from the US for replication, identified an intergenic SNP (rs12700667) on 7p15.2 (overall OR = 1.20, 95% CI 1.13–1.27; $P = 1.4 \times 10^{-9}$)². These two studies did not report replication

of each other's top locus, partly because rs10965235 is monomorphic in Caucasian populations. The European study did find association with rs7521902 (OR = 1.16, 95% CI 1.08–1.25, $P = 9.0 \times 10^{-5}$) near the *WNT4* gene on 1p36.12, that was reported to be suggestively associated in the Japanese (OR = 1.20, 95% CI 1.11–1.29, $P = 2.2 \times 10^{-6}$).

Encouraged by the *WNT4* association and with accumulating evidence for many complex traits that the number of discovered variants is strongly correlated with experimental sample size⁶, we sought to increase the ratio of controls to cases in the Australian GWA cohort and to perform a formal meta-analysis of the Australian (QIMR), UK (OX) and Japanese (BBJ) GWA data.

To increase the power of the Australian GWA dataset we matched the existing QIMR cases and controls² on ancestry to individuals from the Hunter Community Study (HCS)⁷. After stringent quality control (QC), the combined QIMRHCS GWA cohort consisted of 2,262 endometriosis cases and 2,924 controls, increasing the number of controls by 1,054 and the Australian effective sample size by 24%. We also performed more stringent QC incorporating the OX dataset, resulting in a revised OX GWA cohort of 919 endometriosis cases and 5,151 controls. All cases in the QIMRHCS and OX studies have surgically confirmed endometriosis and disease stage from surgical records using the rAFS classification system⁸, subjects are grouped into stage A (stage I or II disease or some ovarian disease with a few adhesions; $n = 1,680$, 52.8%) or stage B (stage III or IV disease; $n = 1,357$, 42.7%), or unknown ($n = 144$, 4.5%). Details of the final GWA and independent replication case-control cohorts are summarized in Table 1 and a schematic of our study design is provided in Fig. 1.

Meta-analysis of all endometriosis 4,604 cases and 9,393 controls for the 407,632 SNPs overlapping in the QIMRHCS, OX and BBJ GWA data, showed that the A allele of rs12700667 at the European 7p15.2 locus (OR = 1.22, 95% CI 1.13–1.31, $P = 7.2 \times 10^{-8}$) also replicates in the Japanese GWA data (OR = 1.22, 95% CI 1.07–1.39, $P = 3.6 \times 10^{-3}$), producing an overall OR of 1.22 (95% CI 1.14–1.30) and $P = 9.3 \times 10^{-10}$ in the GWA meta-analysis; we also confirmed association with allele A of rs7521902 at the 1p36.12 *WNT4* locus (OR = 1.18, 95% CI 1.11–1.25, $P = 4.6 \times 10^{-8}$) (Table 2).

The GWA meta-analysis identified a novel locus on 12q22 near the *VEZT* gene (allele C of rs10859871 OR = 1.18, 95% CI 1.12–1.25, $P = 5.5 \times 10^{-9}$). We also established association with allele G of rs13394619 in the *GREB1* gene on 2p25.1 (OR = 1.12, 95% CI 1.06–1.18, $P = 2.1 \times 10^{-5}$), previously reported (OR = 1.35, 95% CI 1.17–1.56, $P = 3.8 \times 10^{-5}$) in a small independent Japanese GWA study of 696 cases and 825 controls by Adachi et al (2010)⁹. The G allele of rs13394619 approached conventional genome-wide significance ($P = 5 \times 10^{-8}$) in combined analysis of the QIMRHCS, OX, BBJ, Adachi500K and Adachi6.0 GWA data (OR = 1.15, 95% CI 1.09–1.20, $P = 6.1 \times 10^{-8}$) (Table 2). In addition to the three genome-wide significant SNPs on chromosomes 1, 7 and 12 (rs7521902, rs12700667, rs10859871), the Manhattan plot of the all endometriosis GWA meta-analysis results (Supplementary Fig. 1) showed 34 SNPs reached genome-wide *suggestive* association ($P = 10^{-5}$).

Given the substantially greater genetic loading of moderate to severe (Stage B) endometriosis (rAFS stage III or IV disease) compared to minimal (Stage A) endometriosis (rAFS stage I or II disease)², a secondary analysis was performed for the SNPs reaching genome-wide suggestive association, where the association results from QIMRHCS and OX Stage B cases versus controls, were meta-analyzed with the BBJ association results (stage information not available).

After excluding endometriosis cases with minimal (rAFS stage I-II) or unknown severity in the QIMRHCS and OX cohorts, GWA meta-analysis implicated novel loci on 2p14 (allele C of rs4141819 OR = 1.22, 95% CI 1.14–1.32, $P = 6.5 \times 10^{-8}$), 6p22.3 (allele T of rs7739264 OR = 1.21, 95% CI 1.13–1.30, $P = 5.8 \times 10^{-8}$) and 9p21.3 (allele C of rs1537377 OR = 1.22, 95% CI 1.14–1.30, $P = 1.0 \times 10^{-8}$) (Table 2, Supplementary Fig. 2, Supplementary Table 1-2 and Supplementary Note).

Annotated plots showing evidence for association in the combined QIMRHCS, OX and BBJ GWA data of genotyped SNPs across the seven implicated loci from the analysis of all cases and of stage B cases only are provided in Supplementary Figs. 3-9. Imputation up to the 1000 Genomes reference panel produced more significant P values and helped resolve the associated region at the 1p36.12 (rs56318008, $P_{\text{all}} = 1.3 \times 10^{-10}$), 2p25.1 (rs77294520, $P_{\text{stageB}} = 8.6 \times 10^{-8}$), 2p14 (rs2861694, $P_{\text{stageB}} = 7.9 \times 10^{-9}$), 6p22.3 (rs6901079, $P_{\text{all}} = 1.9 \times 10^{-8}$), 9p21.3 (rs7041895, $P_{\text{stageB}} = 5.1 \times 10^{-10}$) and 12q22 (rs11107968, $P_{\text{all}} = 3.9 \times 10^{-9}$) loci (Fig. 2 and Supplementary Figs. 10-16). Of particular note, the most significant imputed SNPs on 1p36.12, rs56318008 and rs3820282 ($P_{\text{all}} = 1.6 \times 10^{-10}$), are located 22 bp 5' and within the *WNT4* gene, respectively.

Interestingly, the most associated genotyped SNP at 9p21.3 (rs1537377) is 55 kb centromeric to the genome-wide significant SNP reported in the original BBJ GWA¹ (rs10965235) located in the *CDKN2BAS* gene, and 49 kb 3' to the transcription end site of *CDKN2BAS*. SNP rs10965235 is monomorphic in Caucasian populations and we investigated the independence of rs10965235 and rs1537377 in the BBJ GWA data. Firstly, in the BBJ GWA data, alleles of rs10965235 and rs1537377 are very weakly correlated, with linkage disequilibrium (LD) metrics of $r^2 = 0.028$ and $D' = 0.461$. Secondly, the allelic association P values for rs10965235 and rs1537377 are $P = 1.6 \times 10^{-4}$ and $P = 1.8 \times 10^{-2}$, respectively. After conditioning on rs10965235, weak residual association remains at rs1537377 ($P = 9.0 \times 10^{-2}$). Consequently, the data suggest there may be two independent genetic risk factors near the *CDKN2BAS* locus on 9p21.3. *CDKN2BAS* is a long non-coding RNA adjacent to and transcribed from the opposite strand to *CDKN2B* (p15), *CDKN2A* (p16) and *ARF* (p14). Loss of heterozygosity of *CDKN2A* and hypermethylation of the *CDKN2A* promoter have been reported in endometriosis^{10,11}.

To further validate the seven SNPs implicated by the meta-analysis, we carried out a replication study using a cohort of 1,044 cases and 4,017 controls obtained from the BioBank Japan independent of the BBJ GWA cohort. As shown in the forest plots of risk allele effects estimated using all cases versus controls (Fig. 3), the effects (ORs) were in the same direction for all seven implicated SNPs across the GWA and replication cohorts. With the exception of rs12700667, which was previously replicated ($P = 1.2 \times 10^{-3}$) in 2,392 cases and 2,271 controls from the US², and rs4141819 (with a marginal $P = 5.1 \times 10^{-2}$), all SNPs were replicated at the nominal $P < 0.05$ threshold (Table 2). All seven SNPs surpass the conventional genome-wide significant threshold of $P = 5 \times 10^{-8}$ after combined analysis of the GWA and replication cases and controls (Table 2). A conservative adjustment of the rs4141819 total P values ($P_{\text{all}} = 8.5 \times 10^{-8}$; $P_{\text{stageB}} = 4.1 \times 10^{-8}$) for performing two independent GWA studies (all and stage B endometriosis cases versus controls) would produce $P > 5 \times 10^{-8}$ ($P_{\text{all-adjusted}} = 1.7 \times 10^{-7}$; $P_{\text{stageB-adjusted}} = 8.2 \times 10^{-8}$). However, the accurately imputed ($R^2 > 0.95$) SNP rs2861694 ($P_{\text{stageB}} = 7.9 \times 10^{-9}$), in strong LD with rs4141819 ($r^2 = 0.981$, $D' = 1.0$; and $r^2 = 0.867$, $D' = 1.0$, in the 379 European and 286 Asian 1000 Genomes reference samples, respectively), would remain genome-wide significant ($P_{\text{stageB-adjusted}} = 1.6 \times 10^{-8}$).

The Q-Q plots for the QIMRHCS, OX and BBJ GWA data (Supplementary Fig. 17a-c) reflect our stringent quality control, while the GWA meta-analysis Q-Q plot (Supplementary

Fig. 17d), reveals a significant preponderance of small P values $<10^{-3}$, suggesting many of these nominally significant SNPs likely represent true signals¹². To further examine the shared genetic risk across our European and Japanese populations we performed polygenic prediction analysis¹³ to evaluate whether the aggregate effects of many variants of small effect in the BBJ GWA cohort, could predict affection status in the European GWA cohorts. The BBJ-derived risk scores significantly predicted affection status in the QIMRHCS ($R^2 = 0.0064$; $P = 6.9 \times 10^{-7}$), OX ($R^2 = 0.0057$; $P = 9.6 \times 10^{-6}$) and combined QIMRHCS+OX all endometriosis case-control sets ($R^2 = 0.0054$; $P = 8.8 \times 10^{-11}$). For the individual and combined QIMRHCS and OX case-control sets, the variance explained peaked in the SNP sets with BBJ GWA $P < 0.1$, using all GWA meta-analysis SNPs (Fig. 4a) and after excluding all SNPs within ± 2500 kb of the seven implicated SNPs listed in Table 1 (Fig. 4b). Analogously, performing the prediction in reverse, the QIMRHCS+OX-derived risk scores significantly predicted affection status in the BBJ case-control set ($R^2 = 0.0106$; $P = 3.3 \times 10^{-6}$) (Supplementary Fig. 18 and Supplementary Note).

A gene-based GWA analysis using VEGAS¹⁴, which accounts for gene size and LD between SNPs, revealed 1,184 genes with a combined $P < 0.05$ and the top three ranked genes associated with endometriosis to be *WNT4* on 1p36.12 ($P = 5.0 \times 10^{-9}$), *VEZT* on 12q22 ($P = 5.7 \times 10^{-7}$) and *GREB1* on 2p25.1 ($P = 2.5 \times 10^{-5}$) (Supplementary Table 3). In addition to having genome-wide significant SNPs near these three genes, the *WNT4* and *VEZT* genes easily surpass our conservative gene-based significant association threshold of $P = 2.85 \times 10^{-6}$ (calculated as $P = 0.05 / 17,538$ independent genes). *WNT4* encodes for wingless-type MMTV integration site family, member 4 and is important for the development of the female reproductive tract¹⁵ and steroidogenesis¹⁶. *VEZT* encodes vezatin, an adherens junction transmembrane protein that is down regulated in gastric cancer¹⁷. *GREB1* encodes growth regulation by estrogen in breast cancer 1, an early response gene in the estrogen regulation pathway involved in hormone dependent breast cancer cell growth¹⁸. For the four remaining implicated regions on 2p14, 6p22.3, 7p15.2 and 9p21.3, no genes were significant ($P = 1.3 \times 10^{-3}$) after adjusting VEGAS results for testing 37 genes across all seven regions, see Table 2, Supplementary Figs. 3-9 and Supplementary Table 4.

In conclusion, given their high gene-based ranking, proximity to genome-wide significant SNPs, known pathophysiology and reported gene expression (Supplementary Note and Supplementary Fig. 19), the *WNT4*, *VEZT* and *GREB1* genes are strong targets for further studies aimed at understanding the molecular pathogenesis of endometriosis. Our results also suggest that a considerable number of SNPs nominally implicated (e.g. $P < 0.1$) in the European and Japanese GWA cohorts represent true endometriosis risk loci. Moreover, the significant overlap in common polygenic risk for endometriosis indicates genetic risk prediction and future targeted disease therapy may be transferred across these populations.

ONLINE METHODS

GWA samples and phenotyping

Initially, 2,351 surgically-confirmed endometriosis cases were drawn from women recruited by The Queensland Institute of Medical Research (QIMR) study¹⁹ and a further 1,030 cases were obtained from women recruited by the Oxford Endometriosis Gene (OXEGENE) study. Australian controls consisted of 1,870 individuals recruited by QIMR² and 1,244 individuals recruited by the Hunter Community Study (HCS)⁷. UK controls encompassed 6,000 individuals provided by the Wellcome Trust Case Control Consortium 2 (WTCCC2). Approval for the studies was obtained from the QIMR Human Ethics Research Committee, the University of Newcastle and Hunter New England Population Health Human Research

Ethics Committees, and the Oxford regional multi-centre and local research ethics committees. Informed consent was obtained from all participants prior to testing².

All Japanese GWA case and control samples were obtained from the BioBank Japan (BBJ) at the Institute of Medical Science, the University of Tokyo. A total of 1,423 cases were diagnosed with endometriosis by the following one or more examinations: multiple clinical symptoms, physical examinations, and laparoscopy or imaging tests. We utilized 1,318 female control samples consisting of healthy volunteers from Osaka-Midosuji Rotary Club, Osaka, Japan and women in the Biobank Japan who were registered to have no history of endometriosis. All participants provided written informed consent to this study. This study was approved by the ethical committees at the Institute of Medical Science, the University of Tokyo and Center for Genomic Medicine, RIKEN Yokohama Institute.

GWA genotyping and quality control (QC)

QIMR and OX cases, and QIMR controls were genotyped at deCODE Genetics on Illumina 670-Quad (cases) and 610-Quad (controls) BeadChips (Illumina Inc), respectively. HCS controls were genotyped at the University of Newcastle on 610-Quad BeadChips (Illumina Inc). The WTCCC2 controls were genotyped at the Wellcome Trust Sanger Institute using Illumina HumanHap1M BeadChips. Genotypes for QIMR cases and controls were called with the Illumina BeadStudio software. Standard quality control procedures were applied as outlined previously²⁰. Briefly, individuals with call rates < 0.95 then SNPs with a mean BeadStudio GenCall score < 0.7 , call rates < 0.95 , Hardy-Weinberg equilibrium $P < 10^{-6}$, and minor allele frequency (MAF) < 0.01 were excluded. Cryptic relatedness between individuals was identified through a full identity-by-state matrix. Ancestry outliers were identified using data from 11 populations of the HapMap 3 and five Northern European populations genotyped by the GenomeEUtwin consortium, using EIGENSOFT^{21,22}. To increase the power of the Australian GWA dataset we ancestrally matched the existing QIMR cases and controls² to individuals from the Hunter Community Study (HCS)⁷ genotyped on Illumina 610 chips. After stringent quality control, the resulting QIMRHCS GWA cohort consists of 2,262 endometriosis cases and 2,924 controls, increasing the Australian effective sample size by 24%.²

Quality control procedures for the OX genotype data resulted in the removal of SNPs with a genotype call rate < 0.99 and/or heterozygosity < 0.31 or > 0.33 . Genome-wide IBS was estimated for each pair of individuals and one individual from each duplicate or related pair (IBS > 0.82) was removed. Genotype data were combined with CEU, CHB&JPT and YRI genotype data from HapMap 3 and individuals of non Northern European ancestry were identified using EIGENSOFT and subsequently removed. SNPs with a genotype call rate < 0.95 were removed, and this threshold was increased to 0.99 for SNPs with MAF < 0.05 . In addition, SNPs showing a significant a) deviation from HWE ($P < 1 \times 10^{-6}$); b) difference in call rate between 58BC and NBS control groups ($P < 1 \times 10^{-4}$); c) difference in allele/genotype frequency between control groups ($P < 1 \times 10^{-4}$); d) difference in call rate between cases and controls ($P < 1 \times 10^{-4}$) and e) a MAF < 0.01 were removed.²

The BBJ cases and controls were genotyped using the Illumina HumanHap550v3 Genotyping BeadChip. Quality control included sample call rate > 0.98 , identity-by-state to exclude close relatedness samples and principal component analysis to exclude non-Asian samples. We also performed SNP quality control (call rate of > 0.99 in both cases and controls and Hardy-Weinberg equilibrium test $P > 1.0 \times 10^{-6}$ in controls); 460,945 SNPs on all chromosomes passed the quality control filters and were further analyzed.¹

GWA meta-analysis

For SNPs passing QC, tests of allelic association (--assoc) were performed using PLINK²³ in the separate QIMRHCS, OX and BBJ GWA datasets. The primary meta-analysis of all endometriosis cases versus controls in the QIMRHCS, OX and BBJ GWA data was performed using a fixed-effect (inverse variance-weighted) model, where the effect size estimates, or β -coefficients, are weighted by their estimated standard errors, utilizing the GWAMA software²⁴.

The threshold of 7.2×10^{-8} for GWA studies of dense SNPs and resequence data²⁵ proposed by Dudbridge and Gusnanto²⁶ was utilized to indicate genome-wide *significant* association, while SNPs with $P = 10^{-5}$ were considered to show a *suggestive* association [as used in the online 'Catalog of Published Genome-Wide Association Studies'].

Also, given the substantially greater genetic loading of moderate to severe (stage B) endometriosis (rAFS stage III or IV disease) compared to minimal (stage A) endometriosis (rAFS stage I or II disease)², a secondary analysis was performed for suggestive SNPs ($P = 10^{-5}$); where the association results from QIMRHCS and OX stage B cases versus controls, were meta-analyzed with the BBJ association results. As previously demonstrated², the exclusion of minimal endometriosis cases has the potential to enrich true genetic risk effects, even taking into account the reduced sample size.

Consistency of allelic effects across studies was examined utilizing the *Cochran's Q* test²⁷. Between-study (effect) heterogeneity was indicated by *Q statistic* P values < 0.1 ²⁸. Meta-analysis of SNPs associated with fixed-effect $P = 10^{-5}$ and showing evidence of effect heterogeneity were also analyzed using the recently developed Han and Eskin's random effects model (RE2) implemented in the Metasoft software²⁹. In contrast to the conventional DerSimonian-Laird random effects (RE) model³⁰, the RE2 model *increases* power under heterogeneity²⁹.

Genotype imputation analysis

In order to assess the impact of variants not present on the Illumina BeadChips and better define the associated regions, we imputed genotypes within ± 2500 kb of the most significant genotyped SNP using the full reference panel from the 1000 Genomes project Interim Phase I Haplotypes (2010-11 data freeze, 2011-06 haplotypes). Imputation was performed separately for the QIMRHCS, OX and BBJ GWA datasets with only the overlapping genotyped SNPs within ± 2500 kb of the most significant genotyped SNP, using the MaCH and minimac programs^{31,32} and following the two-step approach outlined in the online 'Minimac: 1000 Genomes Imputation Cookbook'. Analysis of imputed genotype dosage scores was performed using mach2dat^{31,32} and PLINK. The quality of imputation was assessed by means of the Rsq statistic. Results for poorly imputed SNPs, defined as having an $Rsq < 0.3$, were subsequently removed. The results from association analysis of imputed data in the QIMRHCS, OX and BBJ datasets were then combined via meta-analysis of the β -coefficients weighted by their estimated standard errors using GWAMA.

Replication samples and genotyping

Independent of the BBJ GWA case-control cohort, a total of 1,044 cases and 4,017 controls were obtained from the BioBank Japan and utilized for replication. We note that 653 of these 1,044 cases were also utilized in a small GWA study (Adachi et al. 2010) of 696 cases and 825 controls⁹. To utilize all available association data for rs13394619 maximally, given there is incomplete overlap between the Adachi and our replication cases and zero overlap between the controls, we worked with the published results for rs13394619 in Adachi et al

(2010) and the results from comparing our non-overlapping 391 replication cases to our 4,017 replication controls.

The seven SNPs (rs7521902, rs13394619, rs4141819, rs7739264, rs12700667, rs1537377 and rs10859871) reaching genome-wide significance in the GWA meta-analysis were genotyped in the independent Japanese replication cohort using the multiplex PCR-based Invader assay (Third Wave Technologies), as previously described¹.

Replication and total association analyses

Tests of allelic association were performed using PLINK in the independent Japanese replication cohort. Because only the associations in the same direction would be considered as replicated, one-sided *P* values were obtained by halving the standard (two-sided) PLINK *P* values. To determine the total evidence for association, the one-sided replication *P* values were meta-analyzed with the QIMRHCS, OX, BBJ [and Adachi⁹ 500K (290 cases and 262 controls) and 6.0 (406 cases and 563 controls) for rs13394619] GWA *P* values using METAL³³. The *P* values observed in each case-control cohort were converted into a signed *Z*-score. *Z*-scores for each allele were combined across samples in a weighted sum, with weights proportional to the square-root of the sample size for each cohort³⁴. Given that our cohorts have unequal numbers of cases and controls, we utilized the effective sample size, where $N_{\text{eff}} = 4 / (1 / N_{\text{cases}} + 1 / N_{\text{controls}})$ ³³. We also performed meta-analysis of the β -coefficients weighted by their estimated standard errors using GWAMA to estimate the overall odds ratio and 95% CI for the genome-wide significant SNPs.

Polygenic prediction

The aim of the prediction analysis was to evaluate the aggregate effects of many variants of small effect. We summarized variation across nominally associated loci into quantitative scores and related the scores to disease state in independent samples. Although variants of small effect (e.g., genotype relative risk of 1.05) are unlikely to achieve even nominal significance, increasing proportions of “true” effects will be detected at increasingly liberal *P* value thresholds, e.g. $P < 0.1$ (i.e., ~10% of all SNPs), $P < 0.2$, etc. Using such thresholds, we defined large sets of “allele specific scores” in the “discovery” sample of the Japanese BioBank (BBJ) endometriosis case-control set (1,423 cases, 1,318 controls) to generate risk scores for individuals in the “target” sample of the QIMRHCS (2,262 cases, 2,924 controls), OX (919 cases, 5,151 controls) and combined European (QIMRHCS+OX) endometriosis case-control sets (3,181 cases, 8,075 controls). The term risk score is used instead of risk, as it is impossible to differentiate the minority of true risk alleles from the non-associated variants. In the discovery sample, we selected sets of allele specific scores for SNPs with the following levels of significance; $P < 0.01$, $P < 0.05$, $P < 0.1$, $P < 0.2$, $P < 0.3$, $P < 0.4$, $P < 0.5$, $P < 0.6$, $P < 0.7$, $P < 0.8$, $P < 0.9$, $P < 1.0$. For each individual in the target sample, we calculated the number of score alleles that they possessed, each weighted by the log odds ratio from the discovery sample. To assess whether the aggregate scores reflect endometriosis risk, we tested for a higher mean score in cases compared to controls. Logistic regression was used to assess the relationship between target sample disease status and aggregate risk score. Nagelkerke’s pseudo R^2 was used to assess the variance explained. Prediction was performed using all 407,632 SNPs overlapping the QIMRHCS, OX and BBJ GWA datasets, and after excluding the 6,163 SNPs within ± 2500 kb of the seven implicated SNPs listed in Table 1. We also performed the predictions in reverse, using QIMRHCS +OX-derived risk scores to predict affection status in the BBJ case-control set.

Gene-based association analysis

Gene-based approaches can be more powerful than traditional individual-SNP-based approaches in the presence of allelic heterogeneity. Therefore, utilizing the QIMRHCS, OX

and BBJ GWA data, we performed a genome-wide gene-based association study using VEGAS¹⁴. Briefly, for the 407,632 overlapping SNPs, the *P* values from the European GWA study (i.e., FE meta-analysis of QIMRHCS and OX GWA data) and the *P* values from the Japanese (BBJ) GWA study were analyzed separately using VEGAS. The VEGAS test incorporates evidence for association from all SNPs across a gene and accounts for gene size (number of SNPs) and LD between SNPs by using simulations from the multivariate normal distribution. The resulting European and Japanese gene-based *P* values were meta-analyzed using Stouffer's Z-score combined p-value method³⁴. A total of 17,538 genes (including 50 kb 5' and 3' of their transcription start and end site, respectively¹⁴) contained association results for 1 SNP, so a Bonferroni adjusted significance threshold of $P = 2.85 \times 10^{-6}$ (0.05 / 17,538) was utilized to indicate genome-wide gene-based *significant* association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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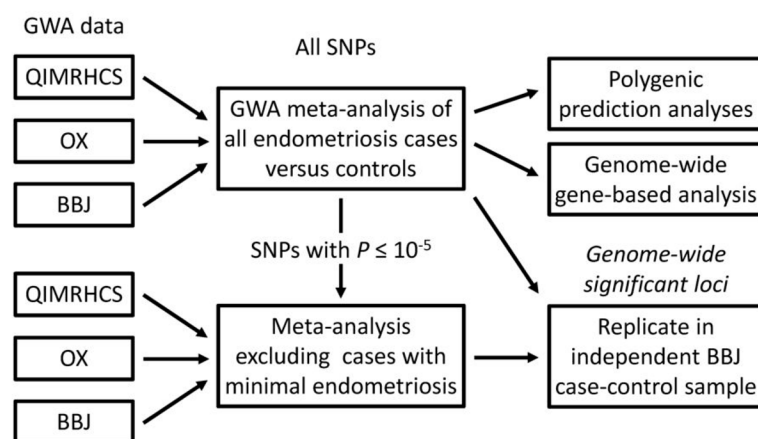
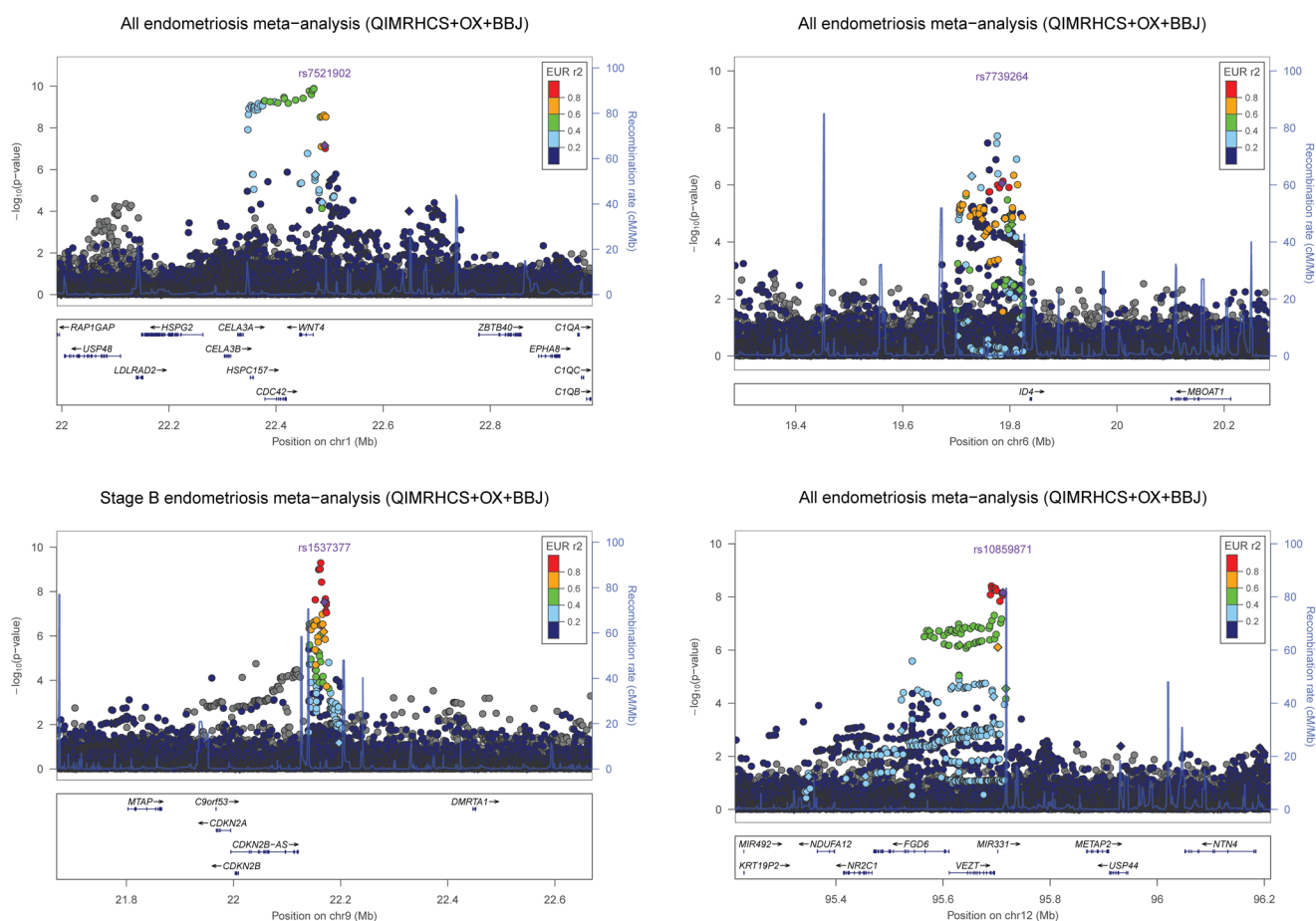
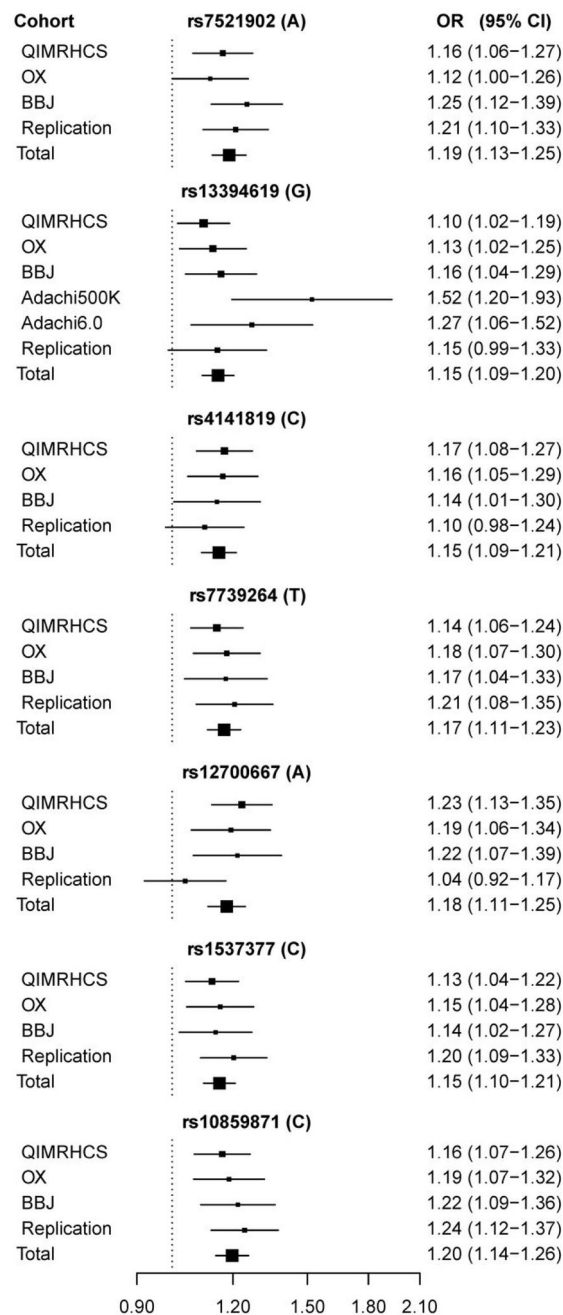


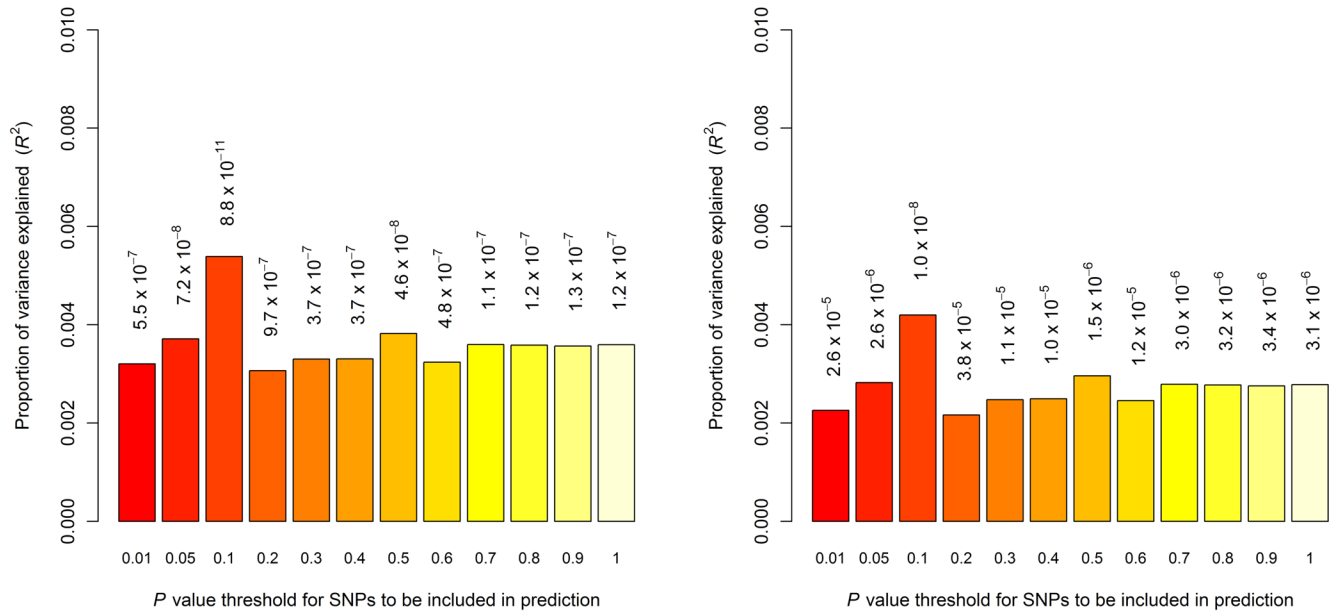
Figure 1.
Study design.

**Figure 2.**

Evidence for association with endometriosis from the QIMRHCS+OX+BBJ GWA meta-analysis across the 1p36.12 (a), 6p22.3 (b), 9p21.3 (c) and 12q22 (d) regions following imputation using the 1000 Genomes Project reference panel. Diamond and circle symbols represent genotyped and imputed SNPs, respectively. The most significant genotyped SNP is represented by a purple diamond. All other SNPs are color coded according to the strength of LD with the top genotyped SNP (as measured by r^2 in the European 1000 Genomes data).

**Figure 3.**

Forest plots of risk allele effects for the seven genome-wide significant SNP loci in the individual and total endometriosis case-control cohorts.

**Figure 4.**

Allele-specific score prediction for endometriosis, using the BBJ population as the discovery dataset and the QIMRHCS+OX population as the target dataset. The variance explained in the target dataset on the basis of allele-specific scores derived in the discovery dataset for twelve significance thresholds ($P < 0.01$, $P < 0.05$, $P < 0.1$, $P < 0.2$, $P < 0.3$, $P < 0.4$, $P < 0.5$, $P < 0.6$, $P < 0.7$, $P < 0.8$, $P < 0.9$, $P < 1.0$, plotted left to right). The y-axis indicates Nagelkerke's pseudo R^2 representing the proportion of variance explained. The number above each bar is the P value for the target dataset prediction analysis (i.e. R^2 significance). Prediction was performed using all GWA meta-analysis SNPs (a) and after excluding all SNPs within ± 2500 kb of the seven implicated SNPs listed in Table 1 (b). These figures show that the results were not driven by a few highly associated regions, indicating a substantial number of common variants underlie endometriosis risk.

Table 1

Summary of the endometriosis case-control cohorts

Cohort	Ancestry	No. of cases (stage B)	No. of controls
QIMRHCS GWA	European	2,262 (905)	2,924
OX GWA	European	919 (452)	5,151
BBJ GWA	Japanese	1,423	1,318
GWA meta-analysis		4,604	9,393
Replication	Japanese	1,044	4,017
Total		5,648	13,410

Table 2
Summary of the GWA and replication study results for the seven genome-wide significant loci

GWA																										
Chr	SNP	Position	RA	OA	QIMRHCs				OX				BBJ				Meta-analysis				Replication				Total	
					RAF _{case}	RAF _{control}	RAF _{case}	RAF _{control}	RAF _{case}	RAF _{control}	RAF _{case}	RAF _{control}	RAF _{case}	RAF _{control}	P _{all}	P _{stageB}	RAF _{case}	RAF _{control}	P	P _{all}	P _{stageB}	P _{all}	P _{stageB}			
1	rs7521902	22490724	A	C	0.265	0.236	0.259	0.238	0.570	0.514	0.514	0.514	0.570	0.514	0.568	0.521	4.6 × 10 ⁻⁸	2.3 × 10 ⁻⁹	6.5 × 10 ⁻⁵	3.2 × 10 ⁻¹¹	0.568	0.521	6.5 × 10 ⁻⁵	3.2 × 10 ⁻¹¹	7.6 × 10 ⁻¹³	
2	rs13394619*	11727507	G	A	0.538	0.514	0.551	0.521	0.485	0.449	0.449	0.449	0.485	0.449	0.489	0.455	6.1 × 10 ⁻⁸	7.0 × 10 ⁻⁸	3.5 × 10 ⁻²	6.1 × 10 ⁻⁹	0.489	0.455	3.5 × 10 ⁻²	6.1 × 10 ⁻⁹	6.7 × 10 ⁻⁹	
2	rs4141819	67864675	C	T	0.331	0.298	0.343	0.309	0.226	0.203	0.203	0.203	0.226	0.203	0.220	0.203	4.0 × 10 ⁻⁷	6.5 × 10 ⁻⁸	5.1 × 10 ⁻²	8.5 × 10 ⁻⁸	0.220	0.203	5.1 × 10 ⁻²	8.5 × 10 ⁻⁸	4.1 × 10 ⁻⁸	
6	rs7739264	19785588	T	C	0.545	0.512	0.556	0.515	0.772	0.742	0.742	0.742	0.772	0.742	0.778	0.744	1.3 × 10 ⁻⁷	5.8 × 10 ⁻⁸	6.9 × 10 ⁻⁴	3.6 × 10 ⁻¹⁰	0.778	0.744	6.9 × 10 ⁻⁴	3.6 × 10 ⁻¹⁰	2.1 × 10 ⁻¹⁰	
7	rs12700667	25901639	A	G	0.769	0.730	0.776	0.744	0.221	0.189	0.189	0.189	0.221	0.189	0.197	0.191	9.3 × 10 ⁻¹⁰	3.8 × 10 ⁻¹¹	2.6 × 10 ⁻¹	3.6 × 10 ⁻⁹	0.197	0.191	2.6 × 10 ⁻¹	3.6 × 10 ⁻⁹	1.1 × 10 ⁻⁹	
9	rs1537377	22169700	C	T	0.424	0.395	0.436	0.401	0.410	0.379	0.379	0.379	0.410	0.379	0.402	0.359	2.5 × 10 ⁻⁶	1.0 × 10 ⁻⁸	1.3 × 10 ⁻⁴	2.4 × 10 ⁻⁹	0.402	0.359	1.3 × 10 ⁻⁴	2.4 × 10 ⁻⁹	5.8 × 10 ⁻¹²	
12	rs10859871	95711876	C	T	0.332	0.299	0.332	0.295	0.373	0.328	0.328	0.328	0.373	0.328	0.377	0.328	5.5 × 10 ⁻⁹	3.7 × 10 ⁻⁷	1.1 × 10 ⁻⁵	5.1 × 10 ⁻¹³	0.377	0.328	1.1 × 10 ⁻⁵	5.1 × 10 ⁻¹³	2.6 × 10 ⁻¹¹	

Chr = Chromosome, Position = GRCh37 (hg19) bp position, RA = risk allele, OA = other allele, RAF = risk allele frequency.

* = GWA meta-analysis and total P values for rs13394619 include results published in Adachi et al. (2010), consisting of $P = 6.1 \times 10^{-4}$ (RAF_{case} = 0.517, RAF_{control} = 0.414) and $P = 1.0 \times 10^{-2}$ (RAF_{case} = 0.488, RAF_{control} = 0.429) obtained in their 500K and 6.0 case-control cohorts, respectively. P_{all} includes all available endometriosis cases. P_{stageB} excludes unknown and minimal (rAFS I-II) endometriosis stage cases where detailed stage data was available.